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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/620,586	07/20/2000	Steen Klysner	0459-0464P	2471

2292 7590 06/30/2004

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 06/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/620,586	KLYSNER ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16,18-23,29 and 53-64* is/are pending in the application.

4a) Of the above claim(s) *3-15,18,55,57 and 59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,16,19-23,29,53,54,56,58 and 60-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/28/04 has been entered.

2. Claims 1-16, 18-23, 29 and 53-64 are pending.

3. Claim 3 -15 , 18, 55, 57 and 59 stand withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 1, 2, 16, 19-23, 29 and 53-54, 56, 58 and 60-64 read on a method for in vivo down-regulation of GDF-8 comprising administering at least one GDF-8 polypeptide, or fragment thereof, or at least one GDF-8 analogue, wherein GDF-8 is derived from bovine GDF-8 polypeptide and wherein the analogue has been modified so that at least one foreign T_H epitope moiety, wherein T cell epitope is Tetanus toxoid epitope is introduced without a carrier molecule, and wherein modification is substitution in SEQ ID NO:12 at amino acid from 49-69 under consideration in the instant application.

In view of the amendment, filed 04/28/04 the following rejection remains:

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1, 2, 16, 19-23, 29 and 53-54, 56, 58 and 60-64 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Barker et al.(US. Pat. No. 6,369,201) in view of the known fact disclosed in the specification on page 16, lines 24-30 and newly cited WO 95/05849 for the same reasons set forth in the previous Office Action, mailed 10/21/03

Applicant's arguments, filed 04/28/04 have been fully considered, but have not been found convincing.

Applicant asserted that: (i) although US Patent '201 disclosed a method for in vivo down regulation of myostatin and the linking of an immunological carrier comprising foreign T_H epitope, such as tetanus toxoid to a myostatin molecule, it does not teach a specific modification of myostatin molecule by inserting a foreign T-helper cell epitope into defined portions of the myostatin polypeptide; (ii) Declaration under 37 C.F.R. by Dr. Klysner indicated that for a person of ordinary skill in the art it would not been obvious to determine the exact position for substitution of the Tetanus toxoid epitope in the myostatin peptide in order tofacilitate the breaking of auto-tolerance.

Applicants have traversed the primary references pointing to the differences between the claims and the disclosure in reference. Applicant is respectfully reminded that the rejection is under 35 USC103. In considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom In re Preda, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968). See MPEP 2144.01. Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY); and In re Burckel 201 USPQ 67 (CCPA).

As was stated in the previous Office Action , US Patent '201 teaches a method for in vivo down-regulation of myostatin (GDF-8) activity, which will result in increase in muscle mass of an animal, comprising administering at least one full length myostatin polypeptide, or at least one myostatin analogue, wherein myostatin is derived from bovine and myostatin immunoconjugate comprising at least one myostatin polypeptide, linked to an immunological carrier (see Abstract and Column 4, especially lines 1-4; column 7 lines 15-22, column 9, lines 22-35, column 13, lines 1-5 in particular). It is noted that US Patent '201 teaches SEQ ID NO:2 that is 100 % identical to SEQ ID NO:12 of the instant application. US Patent '201 teaches that the term "myostatin immunogen" includes polypeptide of myostatin molecule, analogue and modification by substitution such that a substantial fraction of myostatin B cell epitopes are preserved and do not affect the ability of the analog to induces an immunological response (see column 6, lines14-65, column 7, lines 6-15, column 15 lines 1-5, and column 16, lines 42-45 in particular). US Patent '201 teaches a myostatin multimer, wherein modification

includes duplication of at least one myostatin B cell epitope (see column 7, lines 23-30 and column 8, lines 45-65 in particular).
US Patent '201 teaches modification of miostation to include vaccine composition comprising the myostatin polypeptide or analogue and formulated with various adjuvants , such as aluminum adjuvant (see column 24, lines 1-20 in particular) and "immunological carriers" , such as *Tetanus toxoid* epitope, that will enhance the immunogenicity to the molecule and which facilitates breaking of autotolerance (see Column 4, line 10-15, column 9, lines 20-45 in particular). US Patent '201 teaches various method of administering myostatin-containing formulation, including parenteral route (see column 25). US Patent '201 teaches that effective dosages can be readily established by one of ordinary skill in the art through routine trials (see column 25, line 54-56 in particular). US Patent '201 further teach that in order to facilitate breaking of autotolerance to autoantigens myostatin molecule can be modified by association with *Tetanus toxoid* epitope (see column 9, lines 20-45).

US Patent '201 does not explicitly teaches the particular modification of myostatin wherein said molecule has been modified so that at least one foreign T_H epitope moiety, such as *Tetanus toxoid* epitope is introduced at amino acid from 49-69 of myostatin SEQ ID NO:12.

The Known fact disclosed that it is well know in the art various methods of modifying a peptide self-antigen in order to obtain breaking of autotolerance, including introducing into said molecule at least one foreign T cell epitope such *Tetanus toxoid* P2 and P30 epitopes. (see page 16, lines 24-30).

WO '849 disclosed a method for down regulating self-proteins by immunizing with analogues of the self-proteins wherein a number of amino-asid sequences has been substituted with a corresponding number of amino acid sequence which comprisies a foreign T_H epitope, such as *Tetanus toxoid* , while at the same time maintaining the overall tertiary structure of the self-protein in the analogue. (see entire document, Abstract in particular). WO '849 disclosed the advantage of said method, i.e. insertion of T_H epitope into self-protein over the method wherein self-protein is conjugated with *Tetanus toxoid* epitope, to enhance the immunogenicity and facilitates breaking of autotolerance to self-protein (see overlapping pages 4 and 5). WO '849 disclosed insertion of one or more foreign T_H epitopes into a self-protein to induces a profound autoantibody response against said protein (see page 6 in particular).

It would have obvious , conventional and within the skill of a person of ordinary skill in the art at the time the invention was made to identify the exact position for substitution for *Tetanus toxoid* epitope in myostatin molecule in order to facilitates breaking of autotolerance of said molecule and to apply the teaching of the known fact disclosed in the Specification on page 16, lines 24-30 and WO'849 to those of US Patent '201 to obtain a claimed method for in vivo down-regulation of GDF-8 comprising administering one GDF-8 analogue, wherein GDF-8 is derived from bovine GDF-8 polypeptide and wherein the analogue has been modified so that at least one foreign T_H epitope moiety, wherein T cell epitope is Tetanus toxoid epitope is

introduced without a carrier molecule, and wherein modification is substitution in myostatine molecule of SEQ ID NO:12 at amino acid from 49-69.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because it well know in the art that modifying a peptide self-antigen by introducing into said molecule at least one foreign T cell epitope (*Tetanus toxoid* epitope in particular) will facilitates breaking of autotolerance, as taught by the Known fact disclosed in the Specification on page 16, lines 24-30 and WO'849 and can be further used in the method for in vivo down-regulation of myostatin (GDF-8) activity, taught by US Patent '201.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

With regards to Declaration under 37 C.F.R. by Dr. Klysner.

The Examiner disagree with Applicant's statement that for a person of ordinary skill in the art it would not been obvious to determine the exact position for substitution of the *Tetanus toxoid* epitope in the myostatin peptide in order tofacilitate the breaking of auto-tolerance. As obvious from the Known fact disclosed in the Specification on page 16, lines 24-30 and WO'849 the concept of facilitating the breaking of auto-tolerance to self- protein by inserting *Tetanus toxoid* epitope into a specific position in said self-protein while at the same time preserving and maintaining secondary, tertiary and quaternary structure of the peptide was well known in the art at the time the invention was made. Moreover, WO '849 disclosed the advantage of a method wherein T_H epitope is inserted into self-protein over the method wherein self-protein is conjugated with *Tetanus toxoid* epitope to enhance the immunogenicity and facilitates breaking of autotolerance to self-protein. In addition, , Applicant acknowledge that foreign T-helper epitopes have been used to modify peptide self-antigens to destroy autotolerance (see Dr. Klysner decraration page 3 in particular). It is the Examiner position that it requires only routine experimentation for one of ordinary skill in the art at the time the invention was made to identify the exact position for substitution for *Tetanus toxoid* epitope in myostatin molecule in order to facilitates breaking of autotolerance of said molecule.

Claims 20, 21, 23, 60, are included because it would be conventional and within the skill of a person of ordinary skill in the art at the time the invention was made to : (i) determine an effective amount of myostatin polepeptide; or (ii) determine the optimum duration and means of administration. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Claims 29 and 63 are included because the claimed functional limitation would be an obvious properties of the referenced method in vivo down-regulation of myostatin (GDF-8) activity, which will result in increase in muscle mass of an animal, because the reference method using the same method steps and ingredients as the claimed method. It is clear that both the prior art and claimed method administer the same treatment to achieve the same results. When the prior art method is the same as a method described in the specification, it can be assumed the method will obviously perform the claimed process.

5. No claim is allowed

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/272-0840. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/272-0841.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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